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Ceftaroline Fosamil Therapy in Patients With Acute Bacterial Skin and Skin Structure Infections With Systemic Inflammatory Signs: A Retrospective Dose Comparison Across Three Pivotal Trials

G. Ralph Corey , Mark H. Wilcox , Jesus Gonzalez , Alena Jandourek , David J. Wilson , H. David Friedland , Shampa Das , Joseph Iaconis , Matthew Dryden

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### Highlights

- Ceftaroline fosamil treatment in patients with ABSSSI and sepsis
- Post hoc analysis of patients given 600 mg ceftaroline fosamil q12h or q8h
- Clinical cure rates were comparable for both ceftaroline fosamil dosage regimens
- Ceftaroline exposures were not affected by disease severity

ACCEPTED MANUSCRIPT

# Ceftaroline Fosamil Therapy in Patients With Acute Bacterial Skin and Skin Structure Infections With Systemic Inflammatory Signs: A Retrospective Dose Comparison Across Three Pivotal Trials

Running Title: Ceftaroline: Severe Skin Infections

Author(s): G. Ralph Corey,<sup>a</sup> Mark H. Wilcox,<sup>b</sup> Jesus Gonzalez,<sup>c†</sup> Alena Jandourek,<sup>d</sup> David J. Wilson,<sup>c‡</sup> H. David Friedland,<sup>d</sup> Shampa Das,<sup>c§</sup> Joseph Iaconis,<sup>e</sup> Matthew Dryden<sup>f,\*</sup>

Affiliation(s): <sup>a</sup>Department of Medicine, Duke University School of Medicine, 310 Trent Drive, Durham, NC 27710, USA; <sup>b</sup>Department of Medical Microbiology, Leeds Teaching Hospitals & University of Leeds, Leeds, UK; <sup>c</sup>AstraZeneca, Macclesfield, UK; <sup>d</sup>Cerexa, Inc., Oakland, CA, USA; <sup>e</sup>AstraZeneca, Waltham, MA, USA; <sup>f</sup>Royal Hampshire County Hospital, Winchester, UK

<sup>†</sup>Current Address: Block C18-1, 1 Watson Street, Manchester, M3 4EF, UK

<sup>‡</sup>Current Address: DJW STATS Consulting, 1 Market Street, Whaley Bridge, High Peak, UK

<sup>§</sup>Current Address: Centre for Antimicrobial Pharmacodynamics, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Author email addresses: G. Ralph Corey: g.corey@duke.edu; Mark H. Wilcox: Mark.Wilcox@nhs.net; Jesus Gonzalez: tropmedpe@yahoo.com; Alena Jandourek: ajandour@yahoo.com; David J. Wilson: david.wilson@djwstats.co.uk; H. David Friedland: hdavidf22@comcast.net; Shampa Das: shampadaspkpd@gmail.com; <sup>†</sup>Joseph Iaconis: pino.joey@gmail.com; Matthew Dryden: matthew.dryden@hhft.nhs.uk

**Keyword(s):** ceftaroline fosamil; skin and soft tissue infection; sepsis; clinical trial

**\*Corresponding author:**

Matthew Dryden, MA, MBBS, MD, FRCPath  
Department of Microbiology & Infection  
Hampshire Hospitals NHS Foundation Trust  
Romsey Road  
Winchester, Hampshire, SO22 5DG, UK  
Ph: 44(0)1962-824451  
Fax: 44(0) 44(0)1962-825431  
matthew.dryden@hhft.nhs.uk

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**Abstract (word count 250/250)**

**Background:** Post-hoc analysis compared pharmacokinetics and clinical outcomes of ceftaroline fosamil 600 mg every 12 (q12h) versus every 8 hours (q8h), in patients with acute bacterial skin and skin structure infections (ABSSSI) and signs of sepsis.

**Methods:** Clinical outcomes at test-of-cure in patients with ABSSSI and systemic inflammatory signs/systemic inflammatory response (SIRS), and ceftaroline minimum inhibitory concentrations (MICs) against baseline pathogens were compared between COVERS (ceftaroline fosamil 600 mg q8h, 2-h infusion) and the CANVAS 1 and 2 trials (ceftaroline fosamil 600 mg q12h, 1-h infusion). Ceftaroline exposures among patients in COVERS with or without markers of sepsis were compared using population pharmacokinetic (PK) modeling.

**Results:** In COVERS, 62% (312/506) and 41% (208/506) of ceftaroline fosamil-treated patients had  $\geq 1$  systemic sign or SIRS, respectively and 55% (378/693) and 22% (152/693), respectively in the CANVAS trials. Clinical cure rates for the modified intent-to-treat (MITT) population in COVERS and CANVAS were similar for ceftaroline fosamil-treated patients with  $\geq 1$  sign of sepsis (82% [255/312] and 85% [335/394]) and for those with SIRS (84% [168/199] and 85% [131/155]). Ceftaroline MIC distributions were similar across trials. Sepsis did not affect predicted individual steady-state ceftaroline exposures.

**Conclusions:** Clinical cure rates in patients with  $\geq 1$  systemic inflammatory sign or SIRS were comparable for both ceftaroline fosamil dosage regimens. Pathogen susceptibilities to ceftaroline were similar across trials. Ceftaroline exposures were not affected by

disease severity. Ceftaroline fosamil 600 mg q12h is a robust dosage regimen for most ABSSSI patients with sepsis.

**Trial Registry Information:** <https://clinicaltrials.gov>: (NCT01499277, NCT00424190, NCT00423657).

**Keyword(s):** ceftaroline fosamil; skin and soft tissue infection; sepsis; clinical trial

## 1. Introduction (Word count=3130/4000)

Acute bacterial skin and skin structure infection (ABSSSI) and complicated skin and soft tissue infection (cSSTI) include cellulitis/erysipelas, wound infection, and major cutaneous abscess [1, 2] and impose a substantial burden on healthcare systems. Between 2005 and 2010, the incidence of skin and soft tissue infection in the United States was approximately 48 per 1000 person-years [3]; currently, up to 300,000 surgical site infections occur each year, including those in skin and subcutaneous tissue [4]. Skin and soft tissue infections can be serious, requiring hospitalization and surgical procedures, and occasionally can cause bacteremia and death [5]. Factors associated with ABSSSI onset and clinical failures of ABSSSI treatment include obesity and low antibiotic dosage at discharge [6, 7].

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a cephalosporin antibiotic with *in vitro* activity against many of the common bacteria associated with ABSSSI, including *S. aureus* (both methicillin-susceptible [MSSA] and methicillin-resistant [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, and non-ESBL producing *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* [8, 9]. In the

pivotal phase III CANVAS 1 and 2 trials, ceftaroline fosamil 600 mg given as a 1 hour IV infusion every 12 hours (q12h) was shown to be non-inferior to vancomycin plus aztreonam for the treatment of ABSSSI [10-12]. These results supported the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approvals of ceftaroline fosamil 600 mg q12h (adjusted for renal function) for the treatment of adults with ABSSSI and cSSTI, respectively [8, 9].

The presence of sepsis can impact the pharmacokinetics (PK) of some antibiotics and thus potentially affect antibiotic efficacy in patients with ABSSSI. Septic patients in the intensive care unit have shown increased volume of distribution and increased clearance. An increase in volume of distribution in these patients has been shown to be due to capillary leak and endothelial damage, which can result in sub-therapeutic dosing following administration of antibiotics. Clearance is variable and is dependent on the individual's disease state. Variable exposure to drug as a result of changes in volumes and clearance can, in turn, result in variable responsiveness to treatment, in terms of both efficacy and toxicity, and this can impact mortality rates in these patients [13-15].

The phase III COVERS trial was conducted to assess a ceftaroline fosamil dosage regimen of 600 mg as a 2 hour infusion every 8 hours (q8h) in patients with ABSSSI with systemic inflammatory response syndrome (SIRS) or underlying comorbidities and, on average, a greater lesion size [12]. Results from COVERS showed that ceftaroline fosamil 600 mg q8h was non-inferior to vancomycin plus aztreonam in these patients [12]. The objective of this post hoc analysis was to compare ceftaroline fosamil 600 mg q12h versus 600 mg q8h for the treatment of ABSSSI in patients with signs of sepsis, firstly by comparing clinical outcomes and pathogen susceptibilities in the COVERS trial

with the previously published CANVAS trials, and secondly by using population PK modeling to compare ceftaroline exposures in patients with or without markers of sepsis.

## 2. Material and Methods

### 2.1. Study Design

COVERS (NCT01499277) and CANVAS 1 and 2 (NCT00424190 and NCT00423657) were phase 3, multicenter, randomized, double-blind, comparative safety and efficacy trials of IV ceftaroline fosamil versus vancomycin plus aztreonam for the treatment of ABSSSI [10-12]. Patients were randomized to receive ceftaroline fosamil or vancomycin plus aztreonam at a ratio of 2:1 in COVERS and 1:1 in CANVAS 1 and 2. In COVERS, ceftaroline fosamil was administered at 600 mg q8h and vancomycin was administered at 15 mg/kg q12h with aztreonam at 1 g q8h. In CANVAS 1 and 2, ceftaroline fosamil was administered at 600 mg q12h and vancomycin plus aztreonam were each administered at 1 g q12h. Ceftaroline fosamil dosages were adjusted for patients with baseline creatinine clearance (CrCl)  $\leq 50$  mL/min and vancomycin plus aztreonam dosages were adjusted according to respective product labelling and institutional practice guidelines. Treatments were given for 5–14 days in all trials. The primary outcome measure for all three trials was clinical cure rate at test-of-cure (TOC) in the modified intent-to-treat (MITT) and clinically evaluable (CE) patient populations.

### 2.2. Patient and Disease Characteristics

The COVERS and CANVAS trials enrolled adult patients with cSSTI. The entire COVERS patient population, and a proportion of those in the CANVAS trials, met the FDA definition of ABSSSI [1]. Inclusion and exclusion criteria for the CANVAS trials

have been described previously [10, 11]; in brief, patients had a diagnosis of cSSTI (defined as deep extensive cellulitis, major cutaneous abscess requiring surgical drainage, or infected wound, ulcer or burn) of sufficient severity to warrant hospitalization and  $\geq 5$  days of parenteral antibacterial therapy. Inclusion and exclusion criteria for COVERS were similar to the CANVAS trials, with an additional requirement of ABSSSI with surrounding area of erythema, edema, and/or induration with surface area  $\geq 75 \text{ cm}^2$ , reflecting regulatory guidance at the time the study was initiated [1, 12]; of note, COVERS (but not CANVAS) excluded patients with diabetic foot infections. Disease characteristics assessed at baseline included systemic signs of infection, presence of SIRS (defined as presence of  $\geq 2$  of the following symptoms at baseline: temperature  $< 36^\circ\text{C}$  or  $> 38^\circ\text{C}$ ; heart rate  $> 90$  beats per minute; respiratory rate  $> 20$  breaths per minute, or on blood gas, a  $\text{PaCO}_2 < 32 \text{ mmHg}$  [4.3 kPa]; white blood cells [WBCs]  $< 4000 \text{ cells/mm}^3$  or  $> 12,000 \text{ cells/mm}^3$ , or  $> 10\%$  band forms [immature WBC]), and elevated C-reactive protein (CRP) levels. Patients were required to give informed consent prior to enrolment in the trials.

### 2.3. Microbiology

Baseline pathogen susceptibilities to ceftaroline (minimum inhibitory concentrations [MICs]) were determined using Clinical and Laboratory Standards Institute methodology [16] by a central reference laboratory.

### 2.4. Clinical Outcomes

Clinical cure was defined as the total resolution of all signs and symptoms of the baseline infection or improvement such that no further antimicrobial therapy was necessary.



Outcome was determined at the TOC time point (8–15 days after the last dose of study drug) in the MITT population (all randomized patients that received any study medication) and CE population, a subset of the MITT population that had a diagnosis of ABSSSI, had no non-eligible infections, received a prespecified minimum of study drug, had an evaluation at the TOC (or were determined to be a clinical failure at end of therapy), and did not receive any systemically active antibacterial agents that may have affected the infection under study [12, 17]. Clinical cure rates were summarized for the MITT and CE populations overall, and for patient subgroups with  $\geq 1$  systemic sign of inflammation, or sepsis (fever  $>38^{\circ}\text{C}$ , hypothermia  $<36^{\circ}\text{C}$ , elevated WBC count [ $>10,000$  cells/ $\text{mm}^3$  or bands  $>10\%$ ]),  $\geq 2$  severe signs or symptoms (erythema, swelling, tenderness, or warmth that was designated as “severe” by the investigator) or SIRS. As body weight and renal function have also been shown to impact ceftaroline PK [18, 19], clinical cure rates were summarized by body mass index (BMI) and CrCl to compare outcomes across BMI and CrCl subgroups. Finally, clinical cure rates were also summarised by baseline pathogen. Safety was assessed in all randomized patients who received  $\geq 1$  dose of study therapy.

## 2.5. Population Pharmacokinetic Modeling

The ceftaroline population PK model used in this analysis was developed using a large patient PK dataset, which included data from 14 phase I trials in healthy subjects (with normal renal function or renal impairment), one phase II trial in patients with cSSTI, three phase III trials in patients with cSSTI (CANVAS 1, CANVAS 2, and COVERS) and three phase III trials in patients with community-acquired pneumonia [10-12, 19-28]. Patient PK data were obtained in COVERS, and in a subset of 45 patients in CANVAS 1

and 2 trials, by sparse PK sampling over a single dosing interval (ie 8 hours) on Day 3, with intensive PK samples taken in a subset of patients [29]. The population PK model was derived from first-order conditional estimation with the interaction model using the software program, NONMEM version 7.2.0 (ICON plc, Dublin, Ireland). Details related to the PK modeling have been previously described [30]. Ceftaroline PK profiles were estimated for individual patients in COVERS with available ceftaroline PK data. Steady state ceftaroline exposures (maximum plasma concentration [ $C_{\max,ss}$ ] and area under the curve [ $AUC_{ss}$ ]) were derived from the individual predicted ceftaroline concentration-time courses from the population PK model using noncompartmental analysis. To assess whether the presence of markers of systemic inflammation, or sepsis, had any impact on ceftaroline exposures,  $AUC_{ss}$  and  $C_{\max,ss}$  were compared for the following patient subgroups: fever  $\leq 38^{\circ}\text{C}$  or  $>38^{\circ}\text{C}$ , WBC  $\leq 12,000/\text{mm}^3$  or  $>12,000/\text{mm}^3$ , CRP  $\leq 50$  mg/L,  $>50$  to  $\leq 150$  mg/L or  $>150$  mg/L, and presence or absence of SIRS or bacteremia at baseline [29].

## 2.6. Statistical Analyses

Patient outcomes are presented using descriptive statistics and between-group outcome differences (95% CI) were determined using the Miettinen and Nurminen method [31]. Full details of the statistical analyses used in the COVERS and CANVAS 1 and 2 trials have previously been described [10, 11].

## 3. Results

### 3.1. Patient Demographics and Baseline Characteristics

Patient demographics and baseline characteristics are summarized in **Table 1**. Most

patients were male and white. Overall, baseline characteristics, including body mass index, comorbidities, and prior antibiotic therapy, were similar between the patient populations in COVERS and the CANVAS trials. Patients were slightly older in COVERS compared with the CANVAS trials (mean age [SD], 52.6 [16.5] years vs 47.5 [17.0] years for ceftaroline fosamil-treated patients) and there was a greater proportion of patients with a primary cSSTI diagnosis of cellulitis in COVERS (300 [59.3%] vs 249 [35.9%] for ceftaroline fosamil-treated patients).

As expected based on inclusion criteria, more severe ABSSSI was observed in patients in COVERS; median (range) infection area was greater among ceftaroline fosamil-treated patients from COVERS compared with those from CANVAS 1 and 2 (400 [75–5040] cm<sup>2</sup> in COVERS vs 156 [1–3150] cm<sup>2</sup> in CANVAS 1 and 2). A greater proportion of ceftaroline fosamil-treated patients from COVERS also had  $\geq 1$  systemic inflammatory sign (312/506 [61.7%] COVERS vs 378/693 [54.5%] CANVAS 1 and 2) and SIRS (208/506 [41.1%] COVERS vs 152/693 [21.9%] CANVAS 1 and 2) at baseline. Compared with CANVAS 1 and 2, a greater proportion of patients in COVERS had elevated baseline C-reactive protein levels.

### 3.2. Baseline Pathogens

The most common pathogens isolated at baseline in the COVERS patient population were MSSA (n=164 [39%]), MRSA (n=54 [13%]), non-extended-spectrum beta-lactamase-producing *E. coli* (n=26 [6%]), and *S. pyogenes* (n=25 [6%]). In the CANVAS trials, MSSA (n=244 [38%]), MRSA (n=164 [25%]), *S. pyogenes* (n=61 [9%]), and *Enterococcus faecalis* (n=27 [4%]) were most commonly isolated. The proportion of

patients with no baseline pathogen identified was higher in COVERS (n=378 [49.0%]) compared to the CANVAS trials (n=324 [23.2%]), reflecting the higher proportion of patients with cellulitis in the COVERS trial.

Ceftaroline susceptibilities of pathogens isolated at baseline were generally similar between the COVERS and CANVAS trials (**Table 2**). In both COVERS and the CANVAS trials, the ceftaroline MIC (range) and MIC<sub>90</sub> for MSSA isolates were 0.06 to 0.5 mg/L, and 0.25 mg/L, respectively. Ceftaroline susceptibility among MRSA isolates were as follows: COVERS MIC (range), MIC<sub>90</sub>, 0.25–1.0 mg/L, 0.5 mg/L; CANVAS MIC (range), MIC<sub>90</sub>, 0.25–2.0 mg/L, 0.5 mg/L. Ceftaroline MIC (range) and MIC<sub>90</sub> of *S. pyogenes* isolates from COVERS were both  $\leq 0.008$ ; ceftaroline MIC (range) and MIC<sub>90</sub> of *S. pyogenes* isolates from the CANVAS trials were  $< 0.004$  to 0.0008 mg/L and  $\leq 0.004$  mg/L, respectively.

### 3.3. Clinical Outcomes (MITT population)

Overall clinical cure rates at TOC for ceftaroline fosamil were 78.3% (396/506) in the COVERS trial and 85.9% (595/693) in the CANVAS trials. For patients treated with vancomycin plus aztreonam, overall clinical cure rates were 79.2% (202/255) in the COVERS trial and 85.5% (586/685) in the CANVAS trials. Clinical cure rates by inflammatory sign, BMI and CrCl subgroups and overall are summarized in **Table 3**. Clinical cure rates for ceftaroline fosamil-treated patients across all subgroups with systemic inflammatory signs or SIRS were broadly similar in the COVERS and CANVAS trials, ranging from 79% to 85% in COVERS and from 83% to 89% in the CANVAS trials. For comparison, the clinical cure rates for vancomycin plus aztreonam ranged from 72% to 88% in the COVERS trial and from 84% to 90% in the CANVAS

trials. Among ceftaroline fosamil-treated patients with  $\geq 1$  systemic sign of inflammation, or sepsis, clinical cure was observed in 81.7% (255/312) patients in COVERS and 85.0% (335/394) patients in CANVAS 1 and 2. Among ceftaroline fosamil-treated patients with SIRS, clinical cure was observed in 84.4% (168/199) from COVERS and 84.5% (131/155) from CANVAS 1 and 2. Clinical cure rates by inflammatory sign and overall for the CE population were similar to those in the MITT (**Supplemental Table 1**).

Clinical cure rates were generally comparable between ceftaroline fosamil-treated BMI subgroups in the COVERS and CANVAS trials, with the exception of a small number of patients with BMI  $< 18.5$  kg/m<sup>2</sup> (clinical cure rate 8/15 [53.3%] in COVERS compared with 11/15 [73.3%] in CANVAS). Clinical cure rates for ceftaroline fosamil-treated patient subgroups with BMI  $\geq 18.5$  –  $< 25$ ,  $\geq 25$  –  $< 30$  and  $\geq 30$  kg/m<sup>2</sup> ranged from 75.2% to 84.5% in COVERS and 84.5% to 91.2% in the CANVAS trials. A small proportion of ceftaroline fosamil-treated patients had moderate renal impairment (CrCl  $> 30$ – $\leq 50$  mL/min) at baseline in the COVERS and CANVAS trials (31 [6.1%] and 23 [3.3%] respectively). Clinical cure rates for ceftaroline fosamil-treated patients with moderate renal impairment were 23/31 (74.2%) in COVERS and 19/23 (82.6%) in the CANVAS trials. Clinical cure rates for BMI and CrCl subgroups in the CE population were similar to those in the MITT (**Supplemental Table 1**).

Clinical cure rates by baseline pathogen (ME population) are summarized in **Table 4**. Among ceftaroline fosamil-treated patients with infections caused by MSSA, clinical cure rates were 93.6% (88/94) and 93.0% (212/228) in COVERS and CANVAS 1 and 2, respectively. Clinical cure was observed 84.0% (21/25) and 93.4% (142/152) of

ceftaroline fosamil-treated patients with infections caused by MRSA from COVERS and CANVAS 1 and 2, respectively; all MRSA isolates from COVERS and CANVAS 1 and 2 had a ceftaroline MIC of  $\leq 1$  mg/L and  $\leq 2$  mg/L, respectively.

### 3.4. Safety

In COVERS, 45.8% (232/506) of patients treated with ceftaroline fosamil experienced  $\geq 1$  adverse event (AE) compared with 45.5% (116/255) of patients treated with vancomycin plus aztreonam; 44.7% (309/692) of patients treated with ceftaroline fosamil and 47.5% (326/686) of patients treated with vancomycin plus aztreonam experienced  $\geq 1$  AE in the CANVAS trials. The most common AEs among ceftaroline fosamil-treated patients in COVERS (occurring in  $\geq 3\%$  of patients) were nausea (4.0%), headache (3.4%), and hypokalemia (3.0%). The most common AEs among ceftaroline fosamil-treated patients in CANVAS 1 and 2 (occurring in  $\geq 3\%$  of patients) were nausea (5.9%), headache (5.2%), diarrhea (4.9%), pruritus (3.5%), and rash (3.2%).

### 3.5. Population PK Modeling of Cefaroline Exposures

Overall, the population PK modeling dataset included data from 951 subjects, of which 463 were patients with cSSTI. The model described the observed ceftaroline concentration data well, and was considered suitable to calculate exposure parameters for individual patients in COVERS. PK data were available from 371 patients in COVERS for whom a full ceftaroline plasma concentration time-course could be calculated.

Individual predictions of  $AUC_{ss}$  and  $C_{max, ss}$  for these patients are summarised by the presence or absence of fever, SIRS or bacteremia, high WBC count and CRP levels in

**Figure 1.** The individual, median and range  $AUC_{ss}$  and  $C_{max, ss}$  values demonstrated clear

evidence of overlap in patients within the respective disease severity parameters, indicating that these parameters had little effect on the exposures of ceftaroline.

#### 4. Discussion

The COVERS and CANVAS 1 and 2 trials all included patients with systemic signs of inflammation, or sepsis, and SIRS, allowing for an informative comparison of the clinical outcomes associated with ceftaroline fosamil 600 mg as a 1 hour infusion, q8h, versus 600 mg as a 2 hour infusion, q12h in patients with severe ABSSSI. Because the pathogens isolated and their associated ceftaroline susceptibilities in the COVERS trial were similar to the CANVAS trials, we compared the clinical outcomes and pathogen susceptibilities. This provides further rationale for the comparison of clinical outcomes between the trials. Moreover, a patient-rich population ceftaroline PK model, which included data from over 900 subjects, allowed evaluation of predicted ceftaroline exposures for patients with and without sepsis, complementing the clinical data comparisons between the trials.

Although the ceftaroline fosamil q8h dosage regimen was efficacious in COVERS, clinical outcomes among ceftaroline fosamil-treated patient subgroups with more severe disease (ie, >1 systemic sign of inflammation, or sepsis, fever, elevated WBC, or SIRS), were comparable to patients receiving ceftaroline fosamil q12h in the CANVAS trials. Clinical cure rates were also generally comparable for BMI and CrCl patient subgroups in the COVERS and the CANVAS trials. Differences in clinical cure rates for ceftaroline fosamil versus vancomycin plus aztreonam were broadly similar across the trials; for both treatment groups, clinical cure rates were generally numerically lower in COVERS

compared to the CANVAS trials. This is likely due to patients generally having a more severe infection and comorbidities that are not captured in a single subgroup category. Ceftaroline fosamil was well tolerated in both trials, with AEs representative of the cephalosporin class. Hence, the q12h regimen appears robust for the majority of patients with ABSSSI, regardless of the presence of systemic inflammatory signs.

These clinical data are aligned with population PK modeling of individual patients within the COVERS trial, which showed that steady state exposures of ceftaroline were comparable across patients with and without signs of sepsis. The PK of ceftaroline in COVERS were similar to results previously reported for subjects treated with ceftaroline fosamil q12h [18, 32], with a dose-proportional increase in exposure from the q8h dosing used in COVERS [30, 32, 33]. Ceftaroline PK therefore does not appear to be affected by disease severity, suggesting that the ceftaroline fosamil q12h regimen provides adequate exposures in ABSSSI patients with severe disease. Pathogen susceptibilities to ceftaroline were similar between the COVERS and CANVAS trials, with both dosage regimens providing broad coverage against commonly isolated ABSSSI pathogens. The MICs of >95% of baseline isolates across the three trials were at or below respective CLSI and EUCAST susceptibility breakpoints for ceftaroline fosamil 600 mg q12h [16, 34].

Clinical response rates were generally comparable across the COVERS and CANVAS trials for key ABSSSI pathogens, including *S. aureus*. MRSA isolated from COVERS and CANVAS 1 and 2 had ceftaroline MICs of  $\leq 1$  mg/L and  $\leq 2$  mg/L, respectively.

Probability of target attainment (PTA) analyses using the ceftaroline population PK model described above have shown that >95% PTA is predicted with the 600 mg q12h dose regimen for *S. aureus* isolates with MICs up to 2 mg/L [30]. With the 600 mg q8h



dosage regimen, >95% PTA is predicted for *S. aureus* isolates with MICs up to 4 mg/L [30]. In 2017, the EMA label was updated to recommend the use of ceftaroline fosamil 600 mg q8h for cSSTI patients where the causative pathogen is *S. aureus* with a ceftaroline minimum inhibitory concentration (MIC) of 2 or 4 mg/L [8]; such isolates are very rare in the US and Europe [35, 36].

Because individual study patient PK data were not analyzed in this retrospective analysis and individual patients may have different states of disease, this was not described in the CANVAS and COVERS trials. We believe that confounds that do exist in this particular patient population are valid, but given the positive findings in our study, do not appear to play a substantial role in the efficacy or toxicity of ceftaroline treatment. In addition, because this analysis is a retrospective cross-trial comparison, it is limited by the inability to completely control for population differences between trials. Similarly, as enrollment for COVERS and the CANVAS trials occurred in different geographic locations, regional differences in care may have affected the results. However, given that the population PK analyses support the conclusions from the cross-trial comparison, the data overall support that ceftaroline fosamil 600 mg q12h is a robust dosage regimen for the great majority of patients with ABSSSI, including those with sepsis and SIRS.

## 5. Conclusions

On the basis of the clinical, microbiological and population PK modeling comparisons presented here, sepsis did not affect predicted individual steady state ceftaroline exposures. Ceftaroline fosamil 600 mg q12h is a well-tolerated, efficacious dosage

regimen for the majority of patients with severe ABSSSI, regardless of the extent of sepsis.

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\*The authors have associations that may pose a conflict of interest.

**Competing Interests:** G. Ralph Corey has no conflicts to disclose.

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Jesus Gonzalez, David J. Wilson, Shampa Das, and Joseph Iaconis were employees of AstraZeneca at the time of study conduct and analysis.

David J. Wilson, Shampa Das, and Joseph Iaconis are shareholders in AstraZeneca.

Alena Jandourek and H. David Friedland were employees of Cerexa (now a subsidiary of Allergan) at the time of study conduct and analysis.

Matthew Dryden: has received honoraria from and attended advisory boards for Bayer, AstraZeneca, Motif-Bio, Pfizer, Matoke, and MSD.

**Ethical Approval:** For each trial, the clinical study protocol was approved before enrolment of any patient into the trial, including approved by or notification to the national regulatory authority, as required by local regulations. Ethical approval was obtained from the local ethical committee at each study center.

#### **Author Contributions**

**J.G., A.J., D.J.W., H.D.F., S.D., and J.I.** contributed to study design. **D.J.W.** made a substantial contribution to data analyses. **J.I.** made a contribution to data analysis. **M.D.** was involved in study design and data interpretation. **All authors** contributed to data interpretation and to each stage of development of the manuscript and review and approved the final version for submission.

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**Table 1**

Patient Demographics and Baseline Characteristics (MITT Population)

Characteristic	COVERS		CANVAS 1 and 2	
	Vancomycin Plus		Vancomycin Plus	
	Ceftaroline Fosamil n=506	Aztreonam n=255	Ceftaroline Fosamil n=693	Aztreonam n=685
Age, mean (SD), y	52.6 (16.5)	53.6 (16.3)	47.5 (17.0)	48.4 (16.6)
Sex, n (%)				
Female	196 (38.7)	107 (42.0)	249 (35.9)	266 (38.8)
Male	310 (61.3)	148 (58.0)	444 (64.1)	419 (61.2)
Race, n (%)				
White	341 (67.4)	160 (62.7)	506 (73.0)	512 (74.7)
Black or African American	13 (2.6)	13 (5.1)	48 (6.9)	41 (6.0)
Asian	126 (24.9)	64 (25.1)	6 (0.9)	5 (0.7)
American Indian or Alaska Native	1 (0.2)	0	6 (0.9)	4 (0.6)
Native Hawaiian or Other Pacific	—	—	2 (0.3)	2 (0.3)

Islander				
Multiracial/other	25 (4.9)	18 (7.1)	6 (0.9)	7 (1.0)
BMI, median (range), kg/m <sup>2</sup>	26.6 (15.0–50.0)	26.6 (14.0–50.0)	26.9 (14.1–74.1)	27.4 (16.6–66.5)
Baseline CrCl (mL/min) <sup>a</sup>				
>30–≤50	31 (6.1)	17 (6.7)	23 (3.3)	26 (3.8)
>50–≤80	91 (18.0)	46 (18.0)	99 (14.3)	98 (14.3)
>80	362 (71.5)	183 (71.8)	569 (82.1)	559 (81.6)
Baseline C-reactive protein, mg/L				
≤50	178 (35.2)	100 (39.2)	396 (57.1)	387 (56.5)
>50–≤150	178 (35.2)	80 (31.4)	177 (25.5)	166 (24.2)
>150	139 (27.5)	68 (26.7)	98 (14.1)	111 (16.2)
Primary diagnosis of cellulitis	300 (59.3)	136 (53.3)	249 (35.9)	273 (39.9)
Comorbid conditions, n (%)				
Diabetes mellitus	84 (16.6)	38 (14.9)	122 (17.6)	120 (17.5)
Peripheral vascular disease	27 (5.3)	11 (4.3)	93 (13.4)	93 (13.6)
Infection area, median (range), cm <sup>2</sup>	400 (75–5040)	400 (77–6048)	156 (1–3150)	150 (0.04–4950)
Prior antibiotic therapy, n (%)	240 (47.4)	116 (45.5)	276 (39.8)	260 (38.0)

$\geq 1$ systemic inflammatory sign, n (%) <sup>b</sup>	312 (61.7)	166 (65.1)	378 (54.5)	363 (53.0)
$\geq 2$ severe signs and/or symptoms, n (%) <sup>c</sup>	329 (65.0)	165 (64.7)	372 (53.7)	379 (55.3)
SIRS, n (%) <sup>d</sup>	208 (41.1)	113 (44.3)	155 (22.4)	163 (23.8)

BMI=body mass index; MITT=modified intent-to-treat population; SIRS=systemic inflammatory response syndrome.

<sup>a</sup>Eight patients had CrCl  $>20$ – $<30$  mL/min and 22 patients had missing CrCl data in COVERS; 4 patients had CrCl  $\leq 30$  mL/min in CANVAS 1 and 2.

<sup>b</sup>Systemic signs were fever  $>38^{\circ}\text{C}$ , hypothermia  $<36^{\circ}\text{C}$ , elevated WBC count ( $>10,000$  cells/ $\text{mm}^3$ ), or bands  $>10\%$ .

<sup>c</sup>Severe local signs were erythema, swelling, tenderness, or warmth that was designated as “severe” by the investigator.

<sup>d</sup>Systemic inflammatory response syndrome criteria were defined as presence of  $\geq 2$  of the following symptoms at baseline: temperature  $<36^{\circ}\text{C}$  or  $>38^{\circ}\text{C}$ ; heart rate  $>90$  beats per minute; respiratory rate  $>20$  breaths per minute, or on blood gas, a  $\text{PaCO}_2$ ,  $<32$  mmHg (4.3 kPa); WBCs  $<4000$  cells/ $\text{mm}^3$  or  $>12,000$  cells/ $\text{mm}^3$ , or  $>10\%$  band forms (immature WBC).

**Table 2**

Susceptibility of Pathogens Isolated at Baseline to Cefaroline (mMITT population)

Pathogen	COVERS			CANVAS 1 and 2		
	Isolates (n)	MIC range <sup>a</sup>	MIC <sub>90</sub> <sup>a,b</sup>	Isolates (n)	MIC range <sup>a</sup>	MIC <sub>90</sub> <sup>a</sup>
Gram-positive						
<i>Staphylococcus aureus</i> <sup>c</sup>	217	0.06–1	0.5	399	0.06–2	0.5
MSSA	164	0.06–0.5	0.25	235	0.06–0.5	0.25
MRSA	54	0.25–1	0.5	164	0.25–2	0.5
<i>Streptococci</i>						
<i>Streptococcus pyogenes</i> <sup>d</sup>	25	≤0.008	≤0.008	61	≤0.004–0.008	≤0.004
<i>Streptococcus agalactiae</i> <sup>d</sup>	16	≤0.008–0.015	0.015	22	0.008–0.015	0.015
<i>Streptococcus dysgalactiae</i>	12	≤0.008–0.06	0.015	13	≤0.004–0.008	0.008
<i>Streptococcus anginosus</i>	21	≤0.008–0.03	0.03	14	≤0.004–0.06	0.03
group						
<i>Enterococcus faecalis</i>	13	0.5–64	8	27	0.25–16	8

Gram-negative<sup>c</sup>

<i>Escherichia coli</i> (non-ESBL-producing)	26	≤0.015–8	1	23	0.015–>16	1
<i>Klebsiella oxytoca</i>	8	0.03–0.25	–	11	0.03–0.25	0.25
<i>Klebsiella pneumoniae</i>	12	0.06–>32	>32	18	0.03–>16	>16
<i>Morganella morganii</i>	7	0.03–0.12	–	11	0.06–>16	>16
<i>Proteus mirabilis</i>	11	0.03–>32	0.12	16	≤0.008–>16	>16

ESBL=extended-spectrum beta lactamase; MIC=minimum inhibitory concentration; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-susceptible *S. aureus*.

<sup>a</sup>MIC range/MIC<sub>90</sub> expressed in mg/L.

<sup>b</sup>MIC<sub>90</sub> not calculated when n<10.

<sup>c</sup>FDA/CLSI ceftaroline susceptible/resistant breakpoints ≤1/≥4 mg/L.

<sup>d</sup>FDA/CLSI ceftaroline susceptible breakpoint ≤0.5 mg/L.

<sup>e</sup>FDA/CLSI ceftaroline susceptible/resistant breakpoint for *Enterobacteriaceae* ≤0.5/≥2 mg/L [37].

**Table 3**

Clinical Cure Rates at Test-of-Cure Overall and Among Subgroups of Patients with Systemic Signs of Infection, SIRS, and BMI and baseline CrCl categories (MITT Population)

Patient Population	COVERS			CANVAS 1 and 2		
	Ceftaroline Fosamil	Vancomycin Plus Aztreonam	Between-Group Difference	Ceftaroline Fosamil	Vancomycin Plus Aztreonam	Between-Group Difference
	n/N (%)	n/N (%)	(95% CI)	n/N (%)	n/N (%)	(95% CI)
Overall	396/506 (78.3)	202/255 (79.2)	-1.0 (-6.9 to 5.4)	595/693 (85.9)	586/685 (85.5)	0.3 (-3.4 to 4.0)
≥1 systemic sign <sup>a</sup>	255/312 (81.7)	137/166 (82.5)	-0.8 (-7.7 to 6.8)	335/394 (85.0)	326/379 (86.0)	-1.0 (-6.0 to 4.0)
≥2 severe signs or symptoms <sup>b</sup>	259/329 (78.7)	137/165 (83.0)	-4.3 (-11.3 to 3.3)	330/372 (88.7)	332/379 (87.6)	1.1 (-3.6 to 5.8)
Fever	179/211 (84.8)	104/118 (88.1)	-3.3	185/211 (87.7)	181/201 (90.0)	-2.4

			(-10.6 to 4.9)			(-8.6 to 3.8)
Elevated WBC <sup>c</sup>	177/224 (79.0)	75/104 (72.1)	6.9	205/246 (83.3)	213/254 (83.9)	-0.5
			(-2.8 to 17.5)			(-7.1 to 6.0)
SIRS <sup>d</sup>	168/199 (84.4)	83/105 (79.0)	5.4	131/155 (84.5)	140/163 (85.9)	-1.4
			(-3.5 to 15.2)			(-9.4 to 6.5)
Baseline C-reactive protein, mg/L						
≤50	149/178 (83.7)	83/100 (83.0)	0.7	346/396 (87.4)	333/387 (86.0)	1.3
			(-8.0 to 10.5)			(-3.5 to 6.1)
>50 to ≤150	136/178 (76.4)	67/80 (83.8)	-7.4	156/177 (88.1)	138/166 (83.1)	5.0
			(-16.9 to 3.8)			(-2.5 to 12.7)
>150	105/139 (75.5)	49/68 (72.1)	3.5	76/98 (77.6)	95/111 (85.6)	-8.0
			(-8.8 to 16.9)			(-18.9 to 2.5)
BMI, kg/m <sup>2</sup>						
<18.5	8/15 (53.3)	6/9 (66.7)	-13.3	11/15 (73.3)	5/7 (71.4)	1.9
			(-48.2 to 27.4)			



≥18.5–<25	145/185 (78.4)	67/87 (77.0)	1.37 (–8.7 to 12.7)	201/238 (84.5)	182/223 (81.6)	2.8 (–4.0 to 9.8)
≥25–<30	115/153 (75.2)	71/86 (82.6)	–7.4 (–17.5 to 3.8)	197/216 (91.2)	210/227 (92.5)	–1.3 (–6.7 to 3.9)
≥30	125/148 (84.5)	58/73 (79.5)	5.01 (–5.3 to 16.9)	186/222 (83.8)	188/227 (82.8)	1.0 (–6.0 to 7.9)
CrCl, mL/min <sup>c</sup>						
>30–≤50	23/31 (74.2)	10/17 (58.8)	15.37 (–11.61 to 42.57)	19/23 (82.6)	21/26 (80.8)	1.8 (–21.5 to 24.2)
>50–≤80	71/91 (78.0)	38/46 (82.6)	–4.6 (–17.6 to 10.7)	83/99 (83.8)	88/98 (89.8)	–6.0 (–15.8 to 3.7)
>80	288/362 (79.6)	149/183 (81.4)	–1.9 (–8.6 to 5.5)	492/569 (86.5)	475/559 (85.0)	1.5 (–2.6 to 5.6)

BMI=body mass index; SIRS=systemic inflammatory response; WBC=white blood cell.

<sup>a</sup>Systemic signs were fever >38°C, hypothermia <36°C, elevated WBC count (>10,000 cells/mm<sup>3</sup>), or bands >10%.

<sup>b</sup>Severe local signs were erythema, swelling, tenderness, or warmth that was designated as “severe” by the investigator.

<sup>c</sup>>10,000 cells/mm<sup>3</sup>.

<sup>d</sup>Systemic inflammatory response syndrome criteria were defined as presence of  $\geq 2$  of the following symptoms at baseline: temperature  $< 36^{\circ}\text{C}$  or  $> 38^{\circ}\text{C}$ ; heart rate  $> 90$  beats per minute; respiratory rate  $> 20$  breaths per minute, or on blood gas, a  $\text{PaCO}_2$ ,  $< 32$  mmHg (4.3 kPa); WBCs  $< 4000$  cells/mm<sup>3</sup> or  $> 12,000$  cells/mm<sup>3</sup>, or  $> 10\%$  band forms (immature WBC).

<sup>e</sup>Ceftaroline fosamil dosage regimens were adjusted for patients with  $\text{CrCl} > 30$ – $\leq 50$  mL/min. Clinical cure rates for patients with  $\text{CrCl} > 20$ – $< 30$  mL/min (n=8) and patients with missing  $\text{CrCl}$  data (n=22) in COVERS not shown.

**Table 4**

Clinical Cure Rate by Baseline Pathogen (ME Population)

Pathogen	COVERS			CANVAS 1 and 2		
	Ceftaroline	Vancomycin Plus	Between-Group Difference (95% CI)	Ceftaroline	Vancomycin Plus	Between-Group Difference (95% CI)
	Fosamil	Aztreonam		Fosamil	Aztreonam	
	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
Gram-positive						
<i>Staphylococcus aureus</i> <sup>a</sup>	109/119 (91.6)	61/71 (85.9)	5.7 (-3.3 to 16.5)	352/378 (93.1)	336/356 (94.4)	-1.3 (-4.9 to 2.4)
MSSA	88/94 (93.6)	49/57 (86.0)	7.7 (-1.9 to 19.7)	212/228 (93.0)	22/238 (94.5)	-1.6 (-6.3 to 2.9)
MRSA	21/25 (84.0)	12/15 (80.0)	4.0 (-19.8 to 32.2)	142/152 (93.4)	115/122 (94.3)	-0.9 (-7.0 to 5.5)
<i>Streptococci</i>						
<i>Streptococcus</i>	14/15 (93.3)	7/7 (100)	-6.7 (-30.5 to 30.8)	56/56 (100)	56/58 (96.6)	3.9 (-2.3 to 12.6)
<i>pyogenes</i>						
<i>Streptococcus</i>	5/6 (83.3)	7/9 (77.8)	5.6	21/22 (95.5)	18/18 (100)	N/A

<i>agalactiae</i>			(-41.2 to 44.9)			
<i>Streptococcus</i>	9/9 (100.0)	0/0 (0)	N/A	13/13 (100)	15/16 (93.8)	N/A
<i>dysgalactiae</i>						
<i>Streptococcus</i>	16/18 (88.9)	4/4 (100)	-11.1	12/13 (92.3)	15/16 (93.8)	N/A
<i>anginosus</i> group			(-33.4 to 40.6)			
<i>Enterococcus faecalis</i>	4/6 (66.7)	4/5 (80.0)	-13.3	20/25 (80.0)	22/24 (91.7)	-12.6
			(-59.6 to 41.6)			(-34.1 to 8.0)
Gram-negative						
<i>Escherichia coli</i>	11/12 (91.7)	9/10 (90.0)	1.7	20/21 (95.2)	19/21 (90.5)	N/A
			(-28.5 to 34.7)			
<i>Klebsiella oxytoca</i>	4/4 (100.0)	1/1 (100)	N/A	10/12 (83.3)	6/6 (100)	N/A
<i>Klebsiella pneumoniae</i>	5/7 (71.4)	3/4 (75.0)	-3.6	17/18 (94.4)	13/14 (92.9)	N/A
			(-51.1 to 52.1)			
<i>Morganella morganii</i>	4/4 (100)	2/2 (100)	N/A	11/12 (91.7)	5/6 (83.3)	N/A
<i>Proteus mirabilis</i>	6/7 (85.7)	2/2 (100)	-14.3	10/15 (66.7)	20/21 (95.2)	N/A
			(-53.5 to 58.4)			

ESBL=extended-spectrum beta lactamase; ME=medically evaluable; MIC=minimum inhibitory concentration; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-susceptible *S. aureus*; N/A=not applicable.

<sup>a</sup>Patients with MRSA and MSSA were counted only once.

**Figure Legend**

**Figure 1.** Comparison of predicted steady-state ceftaroline fosamil exposures ( $AUC_{ss}$  and  $C_{max,ss}$ ) in individual ABSSSI patients from COVERS (A) with and without SIRS (B) with and without fever (C) with and without high CRP (D) with and without high WBC count and (E) with and without bacteremia. ABSSSI=acute bacterial skin and skin structure infections, CRP=C-reactive protein, SIRS=systemic inflammatory response syndrome.











